The gas chromotograph will develop into a module for more complex analysers for automated sample processing and plant control. The separation time will continue to decrease; in the past there has been limited interest in fast separations but this could change as automated sample processing is developed. Increasing use of coupled techniques such as GC-GC, liquid chromatography-GC, and supercritical fluid chromatography-GC for the separation of complex mixtures will give resolution unachievable by single column operation.

Columns with immobilized phases of a wider range of selectivity than currently exist will be developed. New sorbent (PLOT) columns and hybrid columns with low loadings of liquid phases, special application phases for separating enantiomers and isomers, and columns better able to withstand aqueous samples can be expected.

Further Reading

Adlard ER (ed.) (1995) *Chromatography in the Petroleum Industry*. Amsterdam: Elsevier.

Dyson N (1994) *Chromatographic Integration Methods*, 2nd edn. London: Royal Society of Chemistry.

Ettre LS and Zlatkis A (eds) (1979) *75 Years of Chromatography – A Historical Dialogue*. Amsterdam: Elsevier.

Grob K (1986) *Classical Split and Splitless Injection in Capillary Gas Chromatography*. Heidelberg: Hüthig.

Grob K (1987) *On-Column Injection in Capillary Gas Chromatography*. Heidelberg: Hüthig.

Guiochon G and Guilleman CL (1988) *Quantitative Gas Chromatography for Laboratory Analysis and On-line Process Control*. Amsterdam: Elsevier.

Hill HH and McMinn DG (1992) *Detectors for Capillary Chromatography*. New York: Wiley.

James AT and Martin AJP (1952) Gas–liquid partition chromatography: the separation of volatile fatty acids from formic acid to dodecanoic acid. *Biochemical Journal* 50: 679–690.

Martin AJP and Synge RLM (1941) A new form of chromatogram employing two liquid phases. *Biochemical Journal* 35: 1358–1368.

Poole CF and Poole SK (1991) *Chromatography Today*. Amsterdam: Elsevier.

Rotzsche H (1991) *Stationary Phases in Gas Chromatography*. Amsterdam: Elsevier.

Ion Mobility Mass Spectrometry

D. Young and C. L. P. Thomas, UMIST, Manchester, UK

Copyright © 2000 Academic Press

DropBooks

Introduction

J. J. Thompson made the first ion mobility measurements about a century ago. Modern ion mobility spectrometry (IMS), however, was first described in the early 1970s. The development of the electron-capture detector (ECD) had generated much interest with its impressive limits of detection, and this provoked thoughts of an ionization detector with an additional level of specificity that could operate as a stand-alone instrument. IMS was introduced initially as 'plasma chromatography', and sometimes as 'gaseous electrophoresis'. Such terms invited unrealistic comparisons between established separation techniques and IMS, with its modest resolving power. Superficial similarities to time-of-flight–mass spectrometry meant that IMS was also initially considered as an atmospheric pressure mass spectrometer, but poor mass-mobility correlations disproved this view too. Such unrealistic expectations arose from a lack of understanding of the principles of operation. Furthermore such misunderstandings confronted with complex responses and memory effects observed in many investigations at that time resulted in disillusionment with the technique by many. IMS was generally dismissed as something of a curiosity.

By the late 1970s advances in sample handling (especially for trace levels) and better electronics led to renewed interest in IMS. Drift tubes were redesigned with heated components, which reduced memory effects, and sample introduction systems were re-evaluated, helping to avoid instrument overloads and allow quantitative work. Perhaps most importantly, IMS was evaluated on its own capabilities, rather than simply being compared with existing techniques.

The result was the appearance of the military chemical agent monitor (CAM) – a sensitive, highly selective, inexpensive, and fully portable instrument. The CAM also demonstrated that it was possible to produce IMS systems that could enable untrained personnel to make difficult chemical measurements in a hostile environment. The extent of the use of IMS in chemical agent monitoring is large. At the moment IMS instruments are issued at the platoon level across all the armies of the western alliance, thus making IMS arguably the most common trace VOC detection system in current use. Plans are underway to issue CAM devices to all military personnel.

The success of CAM encouraged further developments both at research and commercial levels, which are continuing with new applications and modifications constantly being suggested and investigated. Since the early 1980s the name 'ion mobility spectrometry' has been almost universally adopted, suggesting the analogy with mass spectrometry but emphasizing its unique operational basis.

IMS Theory and Instrumentation

Overview of Components and Signals

Figure 1 shows a generalized representation of an IMS system. Gas is brought into the reaction region, where ions are formed from the constituents of the gas. Ions of a selected polarity are moved down an electrical potential gradient and periodically

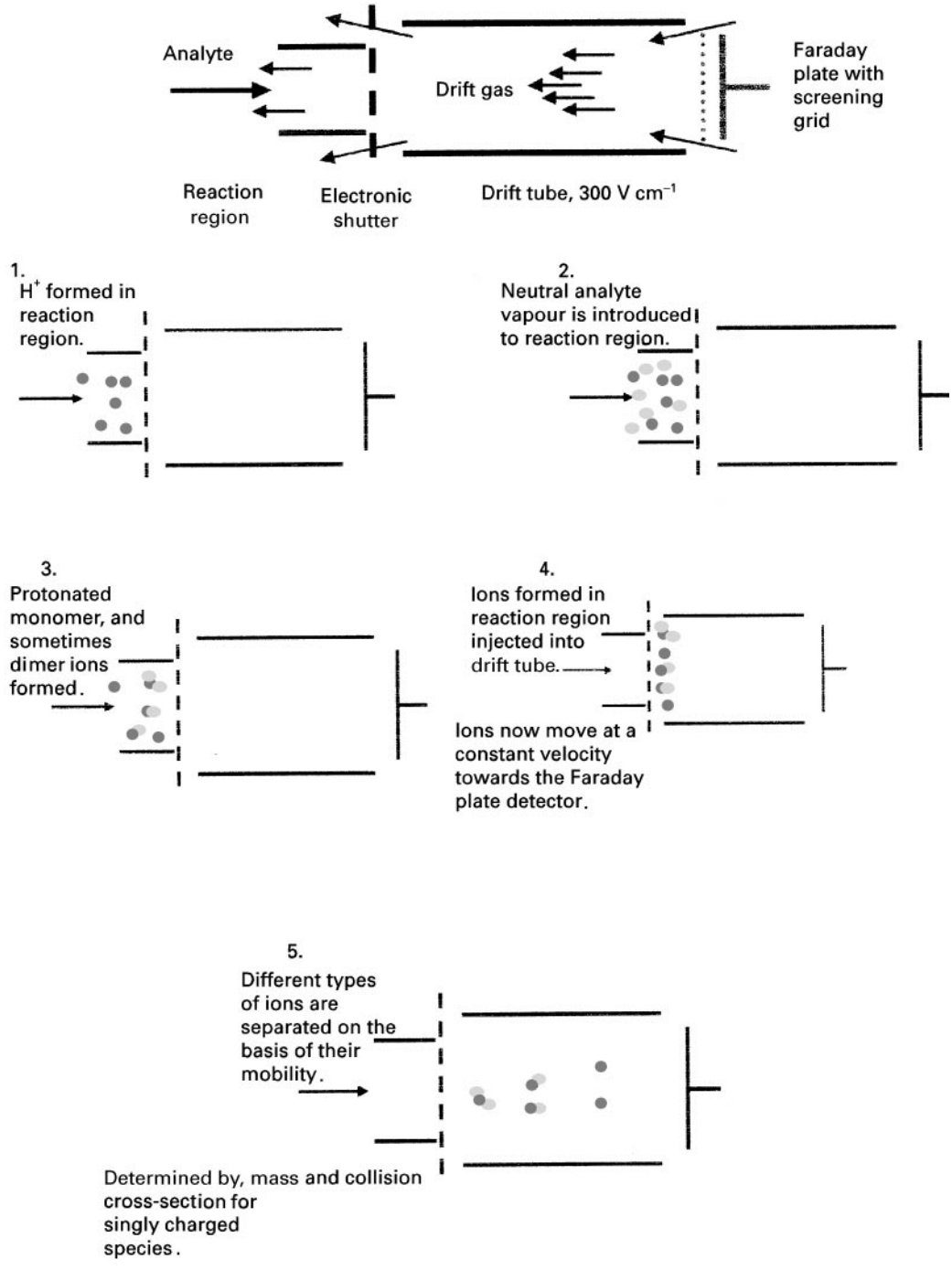
Analyte
Drift gas
Faraday plate with screening grid
Reaction region
Electronic shutter
Drift tube, 300 V cm^{-1}
1.
H^+ formed in reaction region.
2.
Neutral analyte vapour is introduced to reaction region.
3.
Protonated monomer, and sometimes dimer ions formed.
4.
Ions formed in reaction region injected into drift tube.
Ions now move at a constant velocity towards the Faraday plate detector.
5.
Different types of ions are separated on the basis of their mobility.
Determined by, mass and collision cross-section for singly charged species.

Figure 1 A schematic diagram showing the components and operation of IMS.

introduced into the drift region, where they are accelerated by an electric field and slowed by collisions with a countercurrent drift gas flow. Thus the ions attain an average velocity that is dependent, among other things, on the collision cross-section of the ions in the drift gas, the charge on the ion and its mass (see eqns [15]–[19] below). Consequently, different ions achieve different limiting velocities and thus can be separated. Detection is usually by a Faraday plate, leading to current spikes proportional to the number of ions arriving at different times. The resulting trace is referred to as an ion mobility spectrum.

A single mobility spectrum can be generated in the range of 3 to 25 ms, but the signal-to-noise ratio of the spectrum will be low, and small constituents of the spectrum will often be obscured. Thus, for most applications signal averaging is performed, and typically 1–5 s are required to yield an acceptable spectrum. Mobility spectra (**Figure 2**) are characterized by the position and area of the peaks produced by the arriving ion packets at the detector. Overall the response can be evaluated in terms of:

- the magnitude of the signal produced by the reactant ions (this is a measure of the amount of charge in the reaction region of the instrument, and the presence of all analytes in the system); and
- the responses associated with a known analyte (by integrating within a given drift time window).

Thus the amount of signal averaging required, and hence the speed of analysis, depends upon which part of the spectrum is relevant to the analysis and the concentrations of analyte in the sample.

Sample Introduction

As IMS is a vapour-phase analysis technique, it is most commonly used with gaseous or volatile analytes, and analytes are introduced into the reaction region in a carrier gas. This is generally the same gas that is used for the drift flow, and consequently the sample inlet and drift gas flow rates are balanced so that analyte cannot be blown into the drift region.

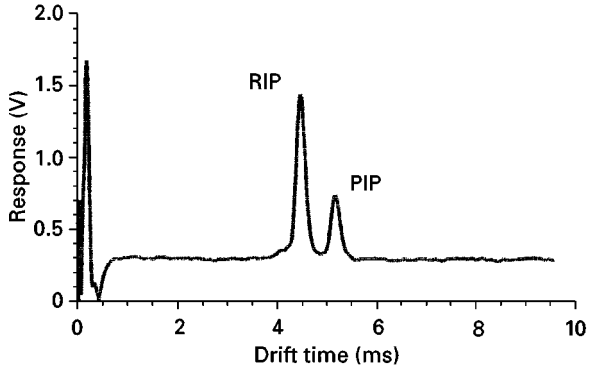

Figure 2 A typical mobility spectrum, showing the reactant ion peak (RIP) from clean air and a product ion peak (PIP) from 2,4-lutidine.

The direct introduction of ambient air is not normally an effective sample introduction technique as the result is high levels of water and traces of ammonia in the reaction region. The high levels of water in ambient air can lead to formation of cluster ions and thus a loss of resolution in the mobility spectra, while ammonia can dominate the spectrum and prevent analyte response owing to its high proton affinity. Consequently a heated dimethylsilicone membrane is frequently used in the inlet. This excludes excessive amounts of water and ammonia from the reaction region but allows analytes to be sampled. This method works effectively with the military IMS units used for CAM. However, the use of a membrane in the inlet increases the response times of the instrument and reduces the sensitivity.

Not surprisingly, IMS has frequently been used with gas chromatography (GC). In fact the first reports of IMS described GC-IMS systems, and some workers still maintain that IMS cannot be effectively used without chromatography for the sample input. GC has been recognized as intrinsically compatible with IMS, as the carrier gas will not generate a response, samples are typically small enough to avoid saturation of the instrument, and pre-separation of analytes simplifies ionization procedures and responses. Interfacing the techniques is also relatively straightforward, although memory effects were initially found to be a problem. This was overcome by introducing the column effluent either laterally or axially after the ionization source (**Figure 3**), and allowing it to be carried back through the ionization region by the drift flow. These unidirectional flow configurations reduce IMS cell clearance times and significantly enhance the response of the instrument.

IMS has also been used for liquid samples. Membranes between the liquid sample and a flowing gas stream have enabled IMS to be used to detect chlorinated hydrocarbons and ammonia in water, for example. However, a recent and important development is the coupling of electrospray to IMS. This has been successfully used with IMS to analyse a wide variety of nonvolatile analytes and liquid samples. The electrospray needle is connected into the ionization region instead of the ^{63}Ni source, and the voltages are applied by a power supply independent of the drift voltage supply. Optimization is required in terms of cell and needle temperatures to improve resolution and avoid vaporization of samples before ionization. The electrospray needle is also insulated

DropBooks

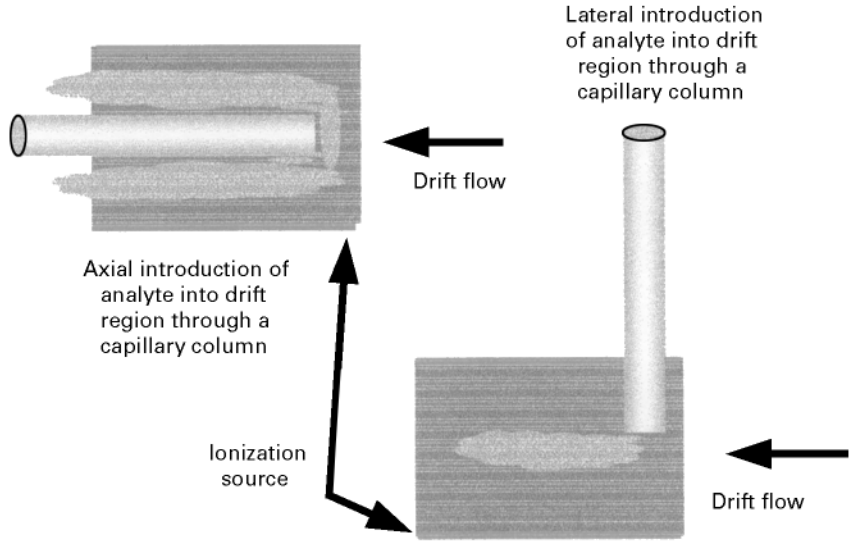
Lateral introduction of analyte into drift region through a capillary column
Drift flow
Axial introduction of analyte into drift region through a capillary column
Ionization source
Drift flow

Figure 3 Methods for interfacing IMS to gas chromatography. Both these arrangements ensure that clear down times in the reaction region are rapid, while at the same time enabling the efficient production of product ions.

to avoid corona discharges. This coupling has been found to provide stable molecular ions and reproducible well-resolved ion mobility spectra.

Several major applications of IMS involve the detection of nonvolatile analytes at trace levels for example narcotics and explosives. In these applications the analysis of the analytes' headspace would not give a satisfactory response. However, thermal desorption of microparticulates of the analytes into a carrier gas stream and analysis with a heated IMS cell provides a highly sensitive and effective alternative that is the basis of several instrument systems used all over the world in support of police, customs, forensic and airline security applications.

Ionization

Currently, the standard ionization source in IMS instrumentation is ^{63}Ni, favoured because it is stable and places no power demands on a portable instrument. A foil is typically used, often electroplated onto gold or platinum. Ionization principles based on this source are well understood, but there are powerful operational incentives to remove radioactive sources from what are primarily designed as portable instruments. Alternative methods include:

- electrospray ionization;
- photoionization using a UV lamp, which produces no reactant ions and limits the analytes which can be studied;
- laser ionization; and
- corona, with latterly, pulsed corona discharge sources that may be configured to behave in a similar manner to ^{63}Ni.

Currently the development of the pulsed corona discharge source appears to be the most promising alternative to radioactivity for general applications as it consumes little power, lasts a long time, operates in both positive and negative mode, and is already being incorporated into the next generation of miniaturized IMS instruments.

Ionization of the gases in the reaction region is perhaps usefully described in terms of ^{63}Ni, as this is the most widely studied and best-understood ionization source. The first step is direct ionization of the carrier gas by the β-particles emitted by the source, which triggers off a multistage reaction leading to the formation of stable reactant ion species. The following example is for the positive-mode ions in air, or nitrogen with low moisture content:

$$N_2 + e^- \rightarrow N_2^+ + 2e^- \quad [1]$$

$$N_2^+ + 2N_2 \rightarrow N_4^+ + N_2 \quad [2]$$

$$N_4^+ + H_2O \rightarrow 2N_2 + H_2O^+ \quad [3]$$

$$H_2O^+ + H_2O \rightarrow H_3O^+ + OH \quad [4]$$

$$H_3O^+ + H_2O + N_2 \rightarrow H^+(H_2O)_2 + N_2 \ \ldots \text{ etc.} \quad [5]$$

The dominant positive-mode reactant ions in clean air will thus be $(H_2O)_nH^+$, where n will be dependent on the moisture content of the gas as well its pressure and temperature. Minor contributions are also generally seen from $(H_2O)_nNH_4^+$ and $(H_2O)_nNO^+$.

An analogous reaction scheme occurs for the negative ions, resulting in $(H_2O)_nO_2^-$ and some $(H_2O)_nCO_4^-$.

When analyte vapours are present in the source region, they may undergo collisional charge transfer reactions with the reactant ions to form product ions in atmospheric pressure chemical ionization (APCI) processes. In almost every case molecular ions are formed in IMS, as APCI causes little fragmentation. Some analyte fragmentation has been observed in IMS, although this has been attributed to thermal decomposition. Typical reaction pathways may be summarized as:

Proton transfer

$$RH^+ + P \rightarrow R + PH^+ \quad [6]$$

Cluster formation

$$R^+ + nP \rightarrow R^+ \cdot P_n \quad [7]$$

Electron capture

$$R^- + P \rightarrow R + P^- \quad [8]$$

Dissociative electron capture

$$R^- + MP \rightarrow R + M + P^- \quad [9]$$

Cluster formation

$$R^- + nP \rightarrow R^- \cdot P_n \quad [10]$$

Proton abstraction

$$R^- + PH \rightarrow RH + P^- \quad [11]$$

where R is the reactant ion species, P is the product ion species and M is a neutral fragment.

When any of these reactions occur, the mobility spectrum changes, the size of the reactant ion peak (RIP) reduces as the charge reservoir is depleted, and a new peak, the product ion peak (PIP), appears corresponding to the analyte ion (see Figure 2). These peaks will rise and fall in a synergistic relationship, and as charge is conserved in IMS, the summed peak areas of the mobility spectrum should remain constant throughout these changes.

As analyte concentration increases some polar compounds (e.g. esters and alcohols) form a second PIP, observed at longer drift time, which is due to an ion containing two analyte molecules. This is essentially a clustering reaction forming a proton bound dimer:

Dimer formation

$$PH^+ + P \leftrightarrows P_2H^+ \quad [12]$$

A detailed discussion of the formation of proton bound dimers is beyond the scope of this article. Their appearance in a mobility spectrum is a function of the thermodynamics and kinetics associated with their formation along with their stability in the drift tube. The development of proton-bound dimers is usually associated with highly nonlinear responses associated with the monomer form of the PIP (**Figure 4**).

The formation of product ions occurs rapidly with one or two simple reactions, while the formation of reactant ions is a comparatively slow multi-step process. Once the analyte concentration rises above a critical level the rate of removal of the reactant ions will be faster than their production. This leads to rapid depletion of the charge reservoir in the reactant region, and no further increase in instrument response will be seen. This is referred to as saturation of the instrument, and sets a limit on the response behaviour.

Typical IMS response behaviour with analyte level is shown in Figure 4. The relationship between the instrument response and analyte level for a single-step reaction leading to a product ion may be simply expressed in terms of:

$$RIP_x = RIP_0 \times (e^{-\beta x}) \quad [13]$$

$$PIP_x = RIP_0 \times (1 - e^{-\beta x}) \quad [14]$$

where RIP_0 is the size of the charge reservoir (RIP peak area in the absence of analyte), RIP_x is the RIP area at analyte concentration x, PIP_x is the PIP area at analyte concentration x, β is the 'reactivity coefficient', a function of reaction time and rate constant and x is the analyte concentration.

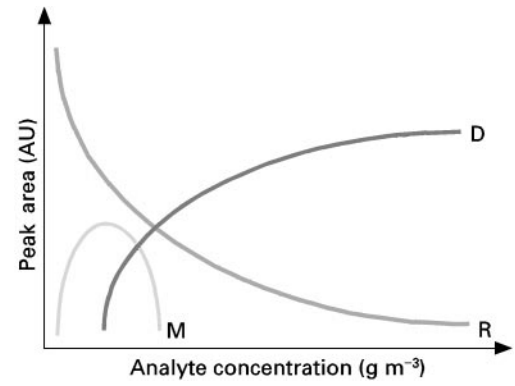

Figure 4 Schematic representation of the relationship between analyte concentration and three IMS peaks: R, reactant ions; M, monomer product ion; and D, dimer product ion.

DropBooks

Attempts to fit linear functions to IMS response trends have shown that linearity can only be approximated (with less than 5% errors) over the first 30–40% of the response range. Quantitative work in the literature suggests that the linear dynamic range of IMS is typically between 1 and 2 orders of magnitude of concentration. Beyond this range quantitation is undertaken on the basis of logarithmic relationships. Eventually, once the reactant ions are depleted, the instrument saturates to a population of product ions.

Working at or near saturation should be avoided. Peaks are frequently seen to broaden and/or their mobility vary as excess neutral analyte molecules cluster around the ions (forming new peaks), or further reactions occur in the drift region (broadening and smearing peaks). An excess of neutral analyte within the instrument also often leads to adsorption onto internal surfaces, such that spurious analyte peaks may be seen for a long time after the original analysis.

Proton or electron transfer can only take place if the proton, or electron, affinity of the neutral molecule is greater than that of the reactant ion. In the default case for positive mode air, the proton is held by water, which has a relatively low proton affinity. This suggests a method by which selectivity can be introduced into the ionization process. If a constant supply of suitably high concentration vapour is provided to the reaction region, then all the protons will be captured to form a new population of reactant ions. This is known as 'doping' the instrument. A dopant can be chosen to have a proton affinity just below that of the target analyte, so that the required response will still be generated but interferences from all compounds with proton affinity lower than the dopant will be prevented. This method has been successfully applied in many laboratory and field applications and has been found to reduce interferences and simplify responses to mixtures, and in some cases to enhance separation and sensitivity. For example acetone is used to dope CAM units, while nicotinamide is the dopant used for narcotics detection and chlorinated volatile organic compounds are used for explosives doping. However, not all compounds are suitable as dopants, for example pyridine-doped systems respond to all compounds (despite pyridine's high proton affinity) and give distorted peaks. This is because clustering reactions rather than charge exchange reactions are occurring.

The concentration of dopant has also been found to be important, as too little does not impart full selectivity (i.e. some 'old' RIP still remains to react), while too much causes cluster formation due to excess neutrals. When doping conditions are optimized then often no changes in PIP position or quantitative behaviour are observed between systems with different dopants.

IMS responses to mixtures can become complicated as components in a mixture compete for charge. The distribution of charge between them tends to be on the basis of concentration and 'reactivity' (e.g. proton or electron affinity). Thus peak areas for analytes in a mixture will not necessarily quantitatively reflect the proportions of each species present in the reaction region. A further problem with mixtures is that 'mixed dimer' ions can be formed, where molecules of two different analytes cluster together around a charge centre. This leads to the appearance of new peaks and more complicated spectra. In these terms the competitive ionization processes can be considered as a source of interferents, in much the same way as overlapping peaks in column chromatography.

In summary, the ionization processes are the cause of some of the major problems of IMS, for example the complicated and congested spectra obtained from mixtures and the limited linear range for many applications. However, they also provide some of the most useful features of the technique such as the spectacular detection limits due to the large number of collisions that occur at atmospheric pressure. Trace levels of analyte are ionized efficiently and the technique is able to respond to a large number of analytes.

Gating the Ions into the Drift Tube

This feature provides IMS with a time-resolved response as opposed to a change in a standing current. An ion shutter is pulsed open for, typically, *c.* 0.2 ms every 5–40 ms, depending on the experimental conditions. The duration that the gate is open is important, as the longer it is open the larger the response (more ions get through) but the broader the ion peaks (greater temporal distribution of identical ions), and hence the lower the resolution will be.

A most important advance has been control of the electric field at the point between the reaction and drift regions with an ion trap. This allows the accumulation of ions between injection pulses rather than their annihilation, with significantly increased sensitivity and much greater control of the ionization processes used to produce the mobility spectra (see **Figure 5**).

Drift Region and Ion Mobility

The drift region is a region of uniform electric field that moves the ions towards the detector with a flow of drift gas in the opposite direction to the ion

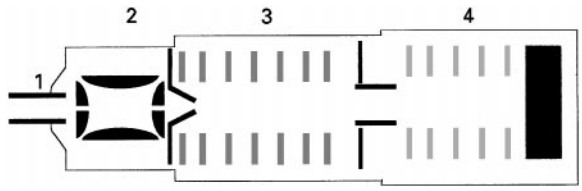

Figure 5 A schematic diagram showing the major systems for ion storage–ion mobility–time-of-flight mass spectrometry.

1. Analytes are ionized and introduced to an ion trap.
2. A tuned ion trap is used to collect ions of a specified mass-to-charge ratio (m/z).
3. The stored ions are injected into a drift tube where they are separated on the basis of their cross-sectional areas.
4. The ions are analysed and quantitated by time-of-flight mass spectrometry.

motion. The drift gas should be inert and free from contaminants, as reactions in the drift region change ion identities and move or broaden peaks. The drift gas also prevents neutrals from the reaction region entering the drift region and undergoing further reactions or clustering.

The electric field is generally provided by a series of conducting field-defining electrodes, and is typically in the range 50–250 V cm^{-1}, which allows weak field approximations to be made with respect to mobility theory, although for many applications it has been shown that the actual value of the electric field is not as important as its homogeneity.

Analytes in IMS are characterized by the drift times of the ions that they form. The mobility of such ions is expressed as:

$$v = \frac{L}{t_d} \qquad [15]$$

$$v = KE \qquad [16]$$

where v is the ion velocity, L is the drift path length, t_d is the drift time, K is the mobility constant, and E is the electric field strength.

Ion mobility is also dependent on temperature and pressure, so these effects can be accounted for by normalizing to a reduced mobility, K_0, enabling comparisons to be made between experiments:

$$K_0 = K\left(\frac{273}{T}\right)\left(\frac{P}{760}\right) \qquad [17]$$

In practice differences in reduced mobility values are still observed due to variations in the internal instrument parameters used in different instruments. Thus the use of mobility standards has been proposed. Currently, 2,4-lutidine, with a K_0 of 1.95 cm^2 V^{-1} s^{-1}, is widely used as it is considered to be relatively unaffected by temperature, clustering or relative humidity. However, dipropyleneglycol monomethylether ($CH_3OC_3H_6OC_3H_6OH$) has also been proposed for similar reasons. Whatever standard is used, reduced mobility values may be calculated as follows:

$$K_{0(an)} = t_{d(an)} \times \left(\frac{K_{0(std)}}{t_{d(std)}}\right) \qquad [18]$$

where (std) refers to values for the standard and (an) refers to values for the analyte under investigation.

The mobility of an ion under weak field conditions is given by:

$$K = \frac{3e}{16N} \times \frac{2\pi^{1/2}}{\mu kT} \times \frac{1}{\Omega} \qquad [19]$$

where e is the ion charge, N is the density of neutral molecules (drift gas), μ is the reduced mass of the ion neutral pair $mM/(m + M)$, k is the Boltzmann constant, T is the temperature of the ions and Ω is the collision cross-section.

Detection

The standard detector in IMS instruments is a simple Faraday plate. The vast majority of IMS instruments have an aperture grid placed *c.* 2 mm forward of the detector. While removal of this feature increases the total signal, it also causes broadening of the peaks, typically from *c.* 0.3 ms to *c.* 3 ms, and thus a loss of resolution. The aperture grid prevents incoming ions from inducing a current in the detector plate. Sensitivity may also be increased by increasing the electric field between the aperture grid and detector to a value significantly higher than that of the standard drift field.

The development of new methods and applications for IMS is greatly eased with the use of a mass spectrometer coupled to the drift cell. IMS-MS has been in routine use in research laboratories since the inception of the technique almost 30 years ago. The instruments are interfaced by using a pinhole aperture to the MS vacuum chamber in the Faraday plate of the ion mobility spectrometer. Such a system can be operated in several modes:

- Total ion monitoring yields the full IMS spectrum.
- Opening the shutters provides a full atmospheric pressure chemical ionization mass spectrometric characterization of the ions in the reaction region.
- Selective ion monitoring enables the contribution of specific species to the mobility spectra to be observed.

DropBooks

An exciting and important development has been the introduction of IMS to ion storage mass spectrometry (Figure 5). This combination of instruments has the potential to isolate selectively trace levels of volatile and nonvolatile materials from a wide range of matrices, identify and quantitate them in a timescale of milliseconds to seconds. The separation speeds reported so far are of the order of greater than 10^6 theoretical plates per minute. Although the approach is still very much in its early stages of development, the potential for vastly increasing the speed of many analyses is considered by many in this field to be a very important factor in the future development of IMS.

Application Areas

Military and Security Applications

The use of IMS to detect chemical warfare agents has already been described. Following on from this application, government research establishments turned their attention to narcotics and explosives. Given the chemical properties of these materials it was not surprising that IMS was found to provide an effective solution to the problem of screening for such materials. Due to the low volatility and trace levels of the substances, these devices use thermal desorption sample introduction systems. The sample is obtained by wiping or vacuuming the surfaces associated with the suspected contamination (for example vehicle interiors, luggage, skin and clothing). Microscopic particles of the analytes are collected onto a filter and thermally desorbed off this medium into the instrument. The devices are installed with a library of spectra and will alarm and identify the substance if a sample produces a matching signal. This method has proven successful at detecting trace levels of a wide range of drugs and explosives materials from a variety of situations, and such devices have become commonplace in airports and at other security checkpoints.

Environmental and Process Monitoring

IMS responds to a vast range of volatile organic compounds as well as inorganic pollutants such as SO_2, HF, NO_x and H_2S. Adaptations of military technology have been used successfully for applications designed to operate in remote and isolated environments (hydrazine monitoring during space shuttle missions, for example). However, the use of IMS as a presumptive monitoring technique for the supervision of pollution prevention measures has yet to be adopted, although research in Europe and the USA has already begun on the technology transfer from the military to the environmental arena.

IMS has also been applied to water monitoring. Solid-phase extraction, membrane thermal desorption and electrospray of environmental water samples have all been developed. No doubt solid phase microextraction will be reported soon as well.

Biological Analytes

The detection and enumeration of bacteria by monitoring for volatiles produced through enzyme–substrate reactions or pyrolysis has been applied to several types of bacteria of water and food hygiene interest (including *Escherichia coli* and *Listeria*). Water, urine and a range of foods have been studied in this way, with significant reduction in analysis times. Given the pedigree of IMS, it is not surprising that aerosol sampling-pyrolysis-GC-IMS systems have been developed for the detection of bacillus spores and other biological warfare agents.

Electrospray-IMS-MS techniques have also been developed for work with biopolymers. These techniques use low-pressure drift tubes (< 10 Torr N_2, He or Ar) and a relatively weak electric field (< 50 V cm^{-1}). An ion trap is most commonly used to inject and concentrate the ions. Although a recent development, this approach has already been used to great effect in the study of sequence and structure relationships. Biomolecular separations of complex mixtures, a protease digest for instance, have also been reported with some success. Variation of the potential used for ion injection has been demonstrated to fragment molecules, which enhances isomer identification and suggests a way to provide high speed sequencing information.

Chromatographic Detection

Combined with chromatography IMS provides an additional dimension to the analysis. It can often separate co-eluting components by mobility, the polarity of the drift tube or their proton or electron affinities. Selected drift time monitoring may be used in an exactly analogous way to selected ion monitoring in mass spectroscopy. Indeed, the development of GC-IMS systems by NASA to monitor continuously the air in the International Space Station has shown that GC-IMS has a near equivalent analytical capability to GC-MS – and one that can be achieved with significantly less complexity and cost. Similar developments are underway with HPLC separation, with sub-picogramme detection limits reported for many compounds. This area of activity is undergoing rapid development and it may be that IMS may come to be used as a general-purpose detection system for chromatography.

The Nature of Mobility Data

So far in this discussion the emphasis has been on assigning a feature in an ion mobility spectrum to the products of a specific ion–molecule reaction. However, there are other ways of using the information contained within a mobility spectrum.

It is possible to study gas-phase reactions and ion–molecule processes within the drift tube with a tuned mass spectrometer. Thus, equilibrium constants for clustering reactions, activation energies for ion–molecule reactants and molecular sizes have all been determined with IMS. The introduction of dopant to the drift region of the instrument enables the reaction kinetics of ion–molecule reactions to be studied and data derived so far from such studies have agreed closely with accepted literature values.

IMS data can also be used in a completely phenomenological-based manner. Complex but constant mixtures yield reproducible ion mobility spectra, although the interpretation and assignment of individual features in such spectra is not currently possible. The application of pattern recognition algorithms and standard chemometric tools enables IMS to be used to identify changes in composition or types of sample. So far identification of different types of polymers, wood species, foodstuffs and pharmaceutical products has been demonstrated. This is an application area that undoubtedly has significant commercial potential.

The Future

Table 1 is a summary of current IMS research areas and applications. The future development of this technique can be seen to fall into three broad areas:

- *The development and improvement of IMS technology*. The problems of instrument saturation, nonlinear responses and complex ambiguous responses are difficult research challenges that will occupy many involved in IMS research and development. New ionization methods and better understanding of the fluid dynamics and kinetics of the ionization process are likely to be important development areas for some time.
- *Sampling interfaces and applications*. Improvements in sampling technology will enable IMS to be exploited in a wider range of contexts. Certainly the successful use of IMS in presumptive testing for narcotics and explosives has interesting possibilities when applied to a wide range of industrial, medical and environmental issues.

DropBooks

Table 1 A summary of current research and application activity in IMS

Analyte	*Application area*	*Comment*
Volatile organic compounds (VOC)	Environmental, process, clinical, and forensic analysis Workplace monitoring Chemical agent monitoring Space craft cabin atmosphere monitoring Extra-terrestrial VOC monitoring	Established areas of operation for IMS. Commercial instruments available that are reliable, rugged and designed for use by the nonspecialist.
	Kinetic and thermodynamic determinations of ion formations, lifetimes and stabilities	Recent development offering rapid measurement techniques for characterizing gas-phase reactions. Not yet applied to larger molecules.
Surfaces, bulk materials	Contaminated soil analysis Surface characterization	Laser ablation and desorption techniques, developed recently, have significantly expanded the scope of applications that IMS may be applied to.
Pesticides	Environmental and process analysis	Electrospray ionization has expanded massively the types of analyte and analysis that may now be undertaken with IMS.
Peptides Sugars Proteins DNA and nucleotides	Life sciences Drug discovery Clinical analysis Foodstuffs characterization	Conformer and isomer separations now routinely achievable. Structure elucidation and fast separations of complex mixtures now a possibility.
Bacteria	Food safety Microbiology Biological warfare Clinical analysis	Pyrolysis techniques offer detection limits of 4 to 5 organisms dm^{-3}, while ELISA approaches are offering fast and highly selective detection methodologies.

- *High speed separations*. The combination of mobility and mass spectrometric technologies described in Figure 5 offers analysis times in the regions of milliseconds to seconds per component. The development of this technology and its application to the life sciences is likely to be a major, perhaps the major, area of IMS development in the medium term. However, the performance of such instrument assemblies has to be offset against their significant capital costs. Miniaturization will play a vital role in this area, reducing the initial outlay required to operate such systems. The work by NASA and the production of GC-IMS databases will continue and it is likely that IMS-based detection systems will become commercially available as alternative approaches to GC-MS.

From the disappointments of the early work with IMS, recent research has yielded substantial advances in this technique. Perhaps the next few years will see the acceptance of IMS as a mainstream analytical approach. Certainly the recent developments in bioseparations have taken many by surprise, and consequently there is a general feeling that the near future will see a huge expansion in the use and application of IMS, particularly in the life sciences.

See also: **I/Mass Spectrometry. II/Chromatography: Gas:** Detectors: Mass Spectrometry; Detectors: Selective. **Mass Spectrometry:** Spectrometry-Mass Spectrometry Ion Mobility.

Further Reading

Carr TW (ed.) (1984) *Plasma Chromatography*. New York: Plenum Press.

Eiceman GA and Karpas Z (1994) *Ion Mobility Spectrometry*. Boca Raton, FL: CRC Press.

Hayhurst CJ, Watts P and Wilders A (1992) Studies on gas-phase negative ion/molecule reactions of relevance to ion mobility spectrometry: mass analysis and ion identification of the negative reactant ion peak in 'clean' air. *International Journal of Mass Spectrometry and Ion Processes* 121: 127–139.

Liu Y, Valentine SJ, Counterman AE, Hoaglund CS and Clemmer DE (1997) Injected-ion mobility analysis of biomolecules. *Analytical Chemistry* 69: 728A–735A.

Rokushika S, Hatano H, Baim MA and Hill Jr, HH (1985) Resolution measurement for ion mobility spectrometry. *Analytical Chemistry* 57: 1902–1907.

St Louis RH and Hill HH (1990) *Critical Reviews in Analytical Chemistry* 5: 321–355.

Watts P (1992) Studies on gas-phase negative ion/molecule reactions of relevance to ion mobility spectrometry: kinetic modelling of the reactions occurring in 'clean' air. *International Journal of Mass Spectrometry and Ion Processes* 121: 141–158.

Zlatkis A and Poole CF (ed.) (1981) *Electron Capture: Theory and Practice in Chromatography*. Amsterdam: Elsevier Scientific.

Large-Scale Gas Chromatography

P. Jusforgues, Prochrom, Champigneulles, France

Copyright © 2000 Academic Press

Introduction

Large scale preparative gas chromatography (GC) is an old established technique: the idea of using a gas chromatographic process to produce pure fractions of a mixture dates back to the 1950s. It took a long time to transform the idea into an efficient and reliable tool for industrial production and, finally, during the 1970s, solutions were found to the crucial problems, and large scale preparative GC became commercially available. At the same time, models were developed to help optimize the separations and to understand the phenomena specific to chromatography at finite concentrations.

The questions raised by large scale preparative GC include the following:

1. What is it?
2. Why is it of interest?
3. How does it work?
4. At what scale?
5. What for (which applications)?
6. How much does it cost?

Principle

Large scale preparative GC uses the same chromatographic principle as analytical GC with packed columns: a carrier gas flows continuously through a column packed with the stationary phase. A pulse of a mixture is injected into the carrier gas at the column inlet and the different components of the mixture are eluted at the column outlet at different times, depending on their volatility and their affinity for the stationary phase. Preparative and analytical GC use the same carrier gases and stationary phases and the same types of detectors.

The goal of preparative GC is not to know the composition of the mixture as in analytical GC but to collect purified fractions for further use. Thus, in large scale preparative GC, for productivity reasons, injected pulses are as large as possible, column